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SCIENTIFIC RESEARCH ON PAPAVER BRACTEATUM

No. 1

Report of the Working Group on Papaver bracteatum [1]

Geneva, 12 - 14 December 1972

[1] This meeting was held with the financial support of the United Nations Fund for Drug Abuse Control

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REPORT OF THE WORKING GROUP ON PAPAVER BRACTEATUM

Papaver bracteatum Lindl., a species of the botanical family Papaveraceae, elaborates thebaine which, by a chemical process, can be converted into codeine.

During recent years, there have been indications of possible shortages of the raw materials for the production of codeine, which is the most widely used anti-tussive and which is also extensively used as a mild analgesic. At present, codeine is mostly derived, by the process of methylation, from the morphine obtained from the opium poppy and about 90 per cent of legally produced morphine is converted into codeine.

With the general reduction in the production of opium (and particularly because of the cessation of poppy cultivation in Turkey) and with the increase in medical care throughout the world, a shortage of codeine could occur which would create a serious problem. Other sources for the production of codeine would be desirable. The United Nations is therefore interested in Papaver bracteatum, which is claimed to be rich in thebaine.

The principle of obtaining codeine from thebaine is already being used in industry[2/], since opium contains appreciable amounts of thebaine - especially the opium from Iran and from South East Asia. Other useful substances (such as naloxone, hydrocodone and oxycodone) may also be derived from thebaine.

A working group of experts on Papaver bracteatum was therefore convened with the financial support of the United Nations Fund for Drug Abuse Control. The group[3/] met in Geneva from 12 to 14 December 1972 in order to review present knowledge of Papaver bracteatum and to prepare guidelines for future research with particular reference to 1973. The group included experts from universities and research institutes and also from interested industrial companies with considerable experience in the field.

2/ Patents have already been issued for this process.

3/ The list of participants is given in Annex I.

Professor J.W. Fairbairn was elected Chairman. Dr. O.J. Braenden represented the Division of Narcotic Drugs and Miss E.S. Lumsden was the Secretary of the Working Group.

The list of suggested aspects for discussion[4] which had been prepared by the Secretariat was adopted.

In the general discussion of present knowledge of Papaver bracteatum, participants described their experiences in this field. Experimental cultivation under varying conditions is being carried out in France, Hungary, Iran, Norway, Turkey, United Kingdom and the United States of America[5]. Although it was premature to judge the results of these experiments, the preliminary findings were encouraging.

P. bracteatum seems to be closely related to P. orientale L., and to P. intermedium O. Ktze. It was not possible in all cases to distinguish between these species of Papaver in the wild state and participants found that, in their early work, seeds provided as P. bracteatum had proved to be P. orientale, yielding practically no thebaine. There seemed to be general agreement that there are adequate morphological, cytological and chemical methods available to identify the thebaine rich strain. However, further research was necessary to confirm this. There may be two chemovars of P. bracteatum - one which produces thebaine almost exclusively and the other which produces thebaine plus alpinigenine. In some cases, oripavine has been found associated with thebaine while in some plants from Iran an alkaloid, as yet unidentified, is present.

Experience so far indicates that the genetic characteristics of P. bracteatum are more important than ecological conditions for the production of plants with a high yield of thebaine.

In Turkey, a good collection had been made of wild varieties of P. bracteatum and related species growing in the eastern districts of the country. These plants are being cultivated in greenhouses and out-of-doors.

4/ See Annex II.

5/ It was noted that the research on P. bracteatum had been initiated at the Institut für Biochemie der Pflanzen in Halle (Saale), where it was continuing and that research was also being carried out in Israel and in other countries.

In France, a study had been made of genetic variability in P. bracteatum and considerable morphological variations had been found. Plants of this Papaver species are relatively easily reproduced vegetatively and root cutting seems a good method of propagation since about one hundred individuals may be obtained from the same plant. Investigations are being made to produce suitable strains rich in thebaine.

Experimental cultivation is also being carried out in the United States of America, in which the plant grows well. Similar research is being carried out in Hungary, Norway and the United Kingdom.

It was generally agreed that seeds from Iran had produced the most promising results. P. bracteatum is indigenous to Iran, where it grows in vast areas - on the slopes facing the Caspian Sea, in rocky mountains at altitudes ranging from 2,000 to 3,000 meters above sea level. Very good plants producing almost exclusively thebaine, in high yields (with big capsules), have been found in different localities in Iran and their seeds are being used there for cultivation. Reproduction by root cutting had also been carried out successfully.

In considering the thebaine content of P. bracteatum, it was noted that the highest yield had been obtained in Iran from plants probably several years in age. Old wild roots contained 1.7 to 2.1% thebaine, whereas those from a plant cultivated for ten months contained 0.7%. The capsules contained 0.85 to 1.1% and the stems 0.2 to 0.3%. The latex contained up to 26% thebaine and about 2% of alpinigenine.

The maximum thebaine content of capsules produced in France was 0.8% representing 95 to 100% of the total alkaloids present. In the United Kingdom, the roots contained 0.25% and the aerial parts 0.2%. In the United States of America, 1 to 3% was found in the capsules, 0.6% in the roots, 0.1% in the leaves and 0.2% in the stem, while in Norway up to 0.4% was present in the roots and up to 0.3% in the leaves. It was generally agreed that the thebaine content of the root was similar to that of the capsules.

In the discussions on the most suitable climatic conditions for the cultivation of P. bracteatum, it was suggested that intense sunlight was important and that soil

conditions did not seem to have a marked influence on the thebaine content. The pH of the soil could vary between 6.5 and 7.5.

The growth of the cultivated plant was very slight during the first year and, in general, capsules appeared only in the second year.

Work on seeds, which had been irradiated at the International Atomic Energy Agency in Vienna, showed that doses higher than 40 K.RAD. were lethal. Plants could be produced when doses of 20 - 40 K.RAD. were applied.

P. bracteatum plants rich in thebaine usually had the following characteristics: (a) Bud shape: oval to oblong; (b) Bracts: flower buds closely surrounded by 5 to 8 imbricate bracts with coarsely toothed fringes: one at least of the bracts persists long after the sepals, petals and stamens have been shed; (c) Calyx: covered with coarse, trichomes with a triangular base; (d) Petals: 5 - 6 present; they are deep red with, at the base, one or two prominent black blotches from which black lines extend upwards; petal colour does not fade on storage; (e) Cytology: chromosome number 2n = 14: (f) Chemotaxonomy: petal pigments produce a characteristic pattern after suitable paper chromatography; thin-layer chromatography of extracts of young plants also show a characteristic alkaloidal spectrum.

It was reported that a full investigation was being made of the morphological, anatomical and cytological characteristics of P. bracteatum and related species.

In preparing guidelines for future research, it was agreed that experimental cultivation should continue and that the United Nations Laboratory should act as the distribution centre for the material. In the first place. seeds of P. bracteatum from Iran would be provided by the Faculty of Pharmacy of the University of Teheran. This batch of seeds would be used, by the participants of the Working Group and by others interested, to investigate the effect of environment on thebaine content. The thebaine present in various parts of plants produced from these seeds would be determined. The possible presence of other alkaloids should also be studied. To add value to this work, the climatic conditions during growth, in each environment, should be recorded wherever possible. To investigate variations within the sample, some of the seeds would be grown in uniform conditions by participants with facilities for such a study.

The Working Group, under the chairmanship of Professor Salemink, also considered practical methods for the determination of thebaine in the various parts of the plant. After discussing the methods currently used by participants, it was suggested that details of these procedures should be forwarded, before 1 February 1973, to the United Nations Laboratory, which would submit its comments on the methods to participants. The methods would be tested on material to be provided by the Faculty of Pharmacy of the University of Teheran and by Francopavot, which would forward adequate samples of the roots, stems, capsules and leaves of P. bracteatum[6/] to the United Nations Laboratory to produce homogenous material for redistribution. It was further recommended to include a study of possible changes in the material during storage.

Investigations should also be made to determine the content of oil, fatty acids, carbohydrates, protein and inorganic matter in the seeds. It was noted that preliminary research indicated that the oil was qualitatively similar to that obtained from the seeds of P. somniferum, and that the seeds of P. bracteatum are consumed by the inhabitants of the mountainous regions of Iran.

The participants of the Working Group felt that the results of this first international discussion on P. bracteatum showed that this plant had considerable potentialities as a source of thebaine, from which codeine and other important substances can be derived. It was, however, obvious that insufficient scientific information was available at present.

The Working Group considered that it would be highly desirable to hold a further meeting in 9 to 12 months' time, in order to assess the results of the proposed scheme of collaborative study and also to plan future research. A rapid accumulation of data would enable an early use to be made of this new source of valuable therapeutic substances.

It was therefore recommended that a further meeting be held and Teheran was suggested as the most suitable venue because this was the geographical centre for this plant and because it would be easily accessible for most interested workers. The third week of September 1973 was suggested as a suitable time for the meeting.

6/ It was also suggested that the flowers should be investigated to determine the possible presence of alkaloids.

ANNEX I

WORKING GROUP ON PAPAVER BRACTEATUM

12 - 14 December 1972

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ANNEX II

WORKING GROUP ON PAPAVER BRACTEATUM

Suggested aspects for discussion

Review of present knowledge of Papaver bracteatum and preparation of guidelines for future research. In this connexion, the following points might be considered:

- the most suitable ecological conditions for the production of Papaver bracteatum with a high yield of thebaine;
- methods of production;
- practical methods for the determination of thebaine in the various parts of the plant;
- the feasibility of research on Papaver bracteatum as a source of substitutes for the edible seeds and oil now obtained from Papaver somniferum;
- the possibility of inducing artificial mutations with a view to developing more productive strains.